MANUFACTURE OF ACETPHENETIDIN FROM PHENOL

BY

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The manufacture of
acetphenetidin from phenol

THE MANUFACTURE OF ACETPHENETIDIN FROM PHENOL

A THESIS

PRESENTED BY

S. R. EVANS and G. T. DOUGHERTY

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OF

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BACHELOR OF SCIENCE

IN

CHEMICAL ENGINEERING

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THE MANUFACTURE OF ACETPHENETIDIN FROM PHENOL

F O R E W O R D

Up to within the last few months, a few patentees have held a monopoly on the manufacture of acetphenetidin, which they tradmarked "Phenacetin." With the expiration of these patents, the original patentees have withheld all information as to the details of operation involved in the manufacture.

The object of this thesis, is therefore, an attempt to learn by laboratory investigation, some of these details.

The authors have chosen Phenol as the starting point, with the idea in view, that, with the probable decline in the price of chemicals used in the process, a method might be worked out to produce acetphenetidin more economically.

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A C K N O W L E D G E M E N T

* * *

The authors are indebted to Professors H. Mc Cormack and B.B. Freud for their advice, suggestions and criticism of the investigation.

THE MANUFACTURE OF ACETPHENETIDIN

FROM PHENOL

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THE MANUFACTURE OF ACETPHENETIDIN FROM PHENOL

Acetphenetidin is the mono-acetyl derivative of para-aminophenetol, and is indirectly a benzene derivative. It is commercially tradmarked "Phenacetin." These two terms are equally divided between the English and German Pharmacoepia.

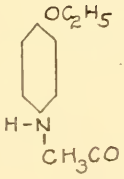
Acetphenetidin is obtained by nitrating Phenol to para- and ortho-Nitrophenol. The para-isomer is now ethylated to para-Nitrophenetol, which is, in turn, reduced by the action of nascent hydrogen, to para-aminophenetol. This body is directly acetylated to acetyl p-phenetidin, or Acetphenetidin.

Acetphenetidin is used as a febrifuge and an antipyretic in medicines. Because of its high restorative powers it is used as an antineuralgic.

Acetphenetidin forms colorless and tasteless white crystals, which have a melting point

of 135°C. These crystals are soluble in alcohol, and sparingly soluble in cold water (one part in 1500.) It was found, on investigation that the crystals are soluble in glycerol, and acetic acid. They are obtained pure by crystallization from hot water.

The formula for Acetphenetidin is:-



NITRATION OF PHENOL

There is a class of compounds, those containing a hydroxyl group, such as Phenol, which react very violently with nitric acid, and are easily oxidized. This action is so energetic, that to obtain the mono-nitro derivative, the acid has, in consequence, to be diluted. The nitration of Phenol by means of dilute nitric acid, has been carried out on a commercial scale, as the para-compound is used in the manufacture of para-amidophenol.

In the presence of such groups as alkyl, hydroxyl, halogen and amino, the entering nitro-group attaches itself to both the ortho and para positions. Thus, in the nitration of Phenol, as the para-compound is the one desired, our problem was to secure as large a yield as possible of the para-nitrophenol.

The three following methods were used in an attempt to determine the relative yields of the para-compound.

METHOD NO. 1

Quantity of reagents used:-

Phenol	240 gr.
Nitric acid (sp. gr. 1.42)	300 c.c.
Water	1020 c.c.

The Phenol (96% pure) was melted, and slowly added in lots of twenty grams every five minutes, to the nitric acid and water, contained in a two-liter beaker. The beaker was surrounded by a four inch water jacket, cooled with a freezing mixture of ice and salt. The contents were thoroughly stirred by an automatic glass stirrer. It took approximately one hour to add all the Phenol. The variation in temperature of the cooling medium and the nitrating mixture is shown in the following table.

On the addition of the Phenol, the liquid immediately changed to a deep brown color, and a dark heavy oil separated out. The mixture was stirred continuously for two and one-half

hours, and then allowed to stand for twelve hours. The heavy oil, containing the ortho- and para-compounds, collected at the bottom of the vessel, and was freed from acid by decanting and pouring into fresh cold water, four times.

In order to separate the two isomers, the dark resinous product was distilled in steam until the distillate was nearly colorless. The ortho-compound distilled over in the form of a yellow oil, solidifying in the receiver, leaving the para-compound mixed with resinous products, in the distilling flask. The para-compound was separated from the tarry residue by extracting with boiling water five times. The united portions of the aqueous extract were then boiled with one-hundred grams of animal charcoal for one hour, and then filtered. The filtrate was then made alkaline with caustic soda solution and concentrated to a small bulk (approximately 600 c.c.) The tarry matter which

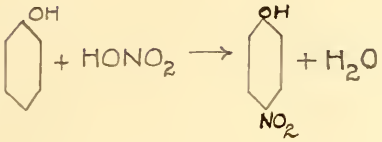
separated out was filtered off through a wet filter. The aqueous solution of the sodium salt was then cooled and allowed to stand for six hours. The separated sodium salt was then filtered, the crystals dissolved in hot water, and the solution made barely acid with hydrochloric acid. The solution was cooled and allowed to stand several hours. The para-nitrophenol crystallized in long colorless needles and was filtered and recrystallized from hot water.

Total yield of o- and p- bodies- - 159.7 gr.
Yield of ortho-nitrophenol - - 140.9 gr.
Yield of para-nitrophenol - - 18.8 gr.

This shows a yield of para-nitrophenol equal to 11.8% of the total reaction products.

The above process takes place according to the following reaction. It is a noteworthy fact, however, that works of many investigators have shown that this reaction does

not take place quantitatively.



NITRATION OF PHENOL

M E T H O D N O. 1.

Time	Temperature of cooler.	Temperature of mixture.
2:30	-10°C	37°C
2:45	- 8	44
3:30	- 5	61.5
3:45	- 2	40.5
4:00	- 2	26.5
4:15	0	18
4:30	0	10
5:00	0	6

METHOD NO. 2.

Quantity of reagents used:-

Phenol	240 gr.
Nitric acid (sp.gr. 1.42)	300 c.c.
Water	1020 c.c.

The Phenol was melted and addes in lots of twenty grams, every five minutes, to the nitric acid and water, without stirring or cooling. The container in this case was a round, two-liter flask. On each addition of Phenol, the contents of the flask were well shaken. When the Phenol was all added, the mixture was allowed to stand for twelve hours.

The subsequent steps in the separation, crystallization and purification of the para-nitrophenol were carried out in the same manner as in Method No.1. The accompanying table indicates the variation in temperature.

The yields were as follows:-

Ortho-nitrophenol	140.1 gr.
Para-nitrophenol	15.1 gr.
Total yield of isomers	155.2 gr.

This method shows a yield of para-nitrophenol equal to 9.75% of the total amount of reaction products. In a comparison of methods Nos. 1 and 2, an increase of 2.05% of the para-nitrophenol was obtained by method No.1 over method No.2. This, then, clearly indicates that of the two foregoing methods, method No.1 is more satisfactory. A further study of increasing the yield leads to the third method.

NITRATION OF PHENOL.

M E T H O D N O. 2.

Time	Temperature of Mixture.
10:00	28°C
10:15	31
10:30	38
10:45	45
11:00	56
11:15	61
11:30	65
11:45	67
12:00	78
12:15	72
12:30	63
12:45	59
1:00	55

METHOD NO. 3.

Quantity of reagents used:-

Phenol	250 gr. (in 25 gr.alcohol)
Sodium nitrate	400 gr.
Water	1000 c.c.
Sulphuric acid (sp.gr.1.84)	500 gr.

The sodium nitrate is dissolved in two hundred grams of water, by heating, and, after cooling, the solution is treated with constant stirring, with five hundred grams H_2SO_4. The container is a two-liter flask, surrounded by a four inch water jacket, cooled with ice and salt mixture, and equipped with automatic stirring apparatus as in method No.1. To the cooled mixture the Phenol and alcohol is added drop by drop from a separatory funnel, with constant stirring. When the Phenol has all been added, the reaction mixture is allowed to stand for two hours, and then treated with double its volume of water. The reaction product, which collects as a dark, heavy oil at the bottom was freed

from acid, distilled in steam, and the para-body recovered from the tarry residue in the distilling flask, as in method No.1.

The aqueous extract was then boiled with one hundred grams animal charcoal for one-half hour, filtered, and the filtrate allowed to stand for twelve hours, when the para-nitrophenol separates out in long, almost colorless needles.

The oil still present in the distilling flask was boiled with a mixture of one part by volume of concentrated HCL, and two parts by volume of water, with the addition of twenty grams of animal charcoal, filtered, and allowed to stand twelve hours. There was thus obtained a second crystallization of para-nitrophenol.

Yields:-

Ortho-nitrophenol	137.8 gr.
Para-nitrophenol	24.5 gr.
Total reaction product	162.3 gr.

This method shows an increase of 3.3% in the yield of the para-compound, over method No.1. These results show that method No.3 is the most satisfactory.

NITRATION OF PHENOL

M E T H O D N O. 3.

Time	Temperature of cooler	Temperature of mixture
11:45	-4°C	16°C
12:00	-4 C	20
12:30	-2 C	22
12:45	-2 C	25
1:00	-3 C	30
1:15	-4 C	26
1:30	-5 C	22
1:45	-3 C	20
2:00	-2 C	18
2:15	0 C	19
2:30	0 C	20

IDENTIFICATION TESTS OF PARA-NITROPHENOL

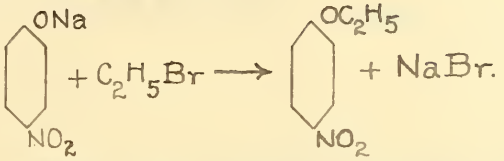
Melting point by capillary tube method was found to be 113.6°C. The melting point of the pure body is 114°C. This discrepancy in temperature is accounted for by the fact that it was impossible to completely separate out all the tarry matter.

Solubility test:- One gram of the substance readily dissolved in 5 c.c. of hot water.

To identify as a nitrophenol:- Dissolve one gram of para-nitrophenol in a solution of sodium carbonate by warming; the scarlet red sodium salt is formed.

ETHYLATION OF P-NITROPHENOL TO P-NITROPHENETOL.

The ethylation is carried on as shown by the following equation:-



Owing to the scarcity of ethyl bromide at the present time, this reagent was prepared in the following manner:-

150 c.c. of distilled water were gradually added to 250 c.c. H_2SO_4(sp.gr. 1.84) and after cooling, 250 c.c. absolute alcohol were run in, care being taken to prevent any great rise in temperature. This was accomplished by constant stirring and cooling. When cold, 200 grams Na Br were added. The whole mixture was then heated on a sand bath in a flask attached to a condenser, and the ethyl bromide distilled over at as low a temperature as possible. This process required eight hours. The ethyl bromide was collected in water, washed with water and dilute sodium carbonate solution,

dried over fused calcium chloride, and re-distilled.

The yield was 100 c.c. of ethyl bromide. It was found that no HBr distilled over with this method.

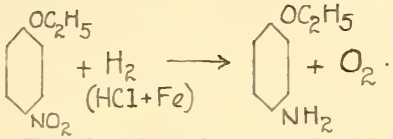
In ethylation, two runs were made, the first one using twenty-five grams para-nitro-phenol, and the second one using thirteen grams. The para nitrophenol was first dissolved in 100 c.c. of hot water, and the solution then made alkaline with NaOH solution in a 500 c.c. erlenmeyer flask. 30 c.c. ethyl bromide were then added to number one, and 15 c.c. to number two. This is an excess of 5 c.c. over molecular proportions in each case. The flasks were then attached to a long reflux condensers and heated on the water bath for seven hours, at which time the ethylation was complete.

The condensers were then disconnected and excess of alcohol and ethyl bromide distilled off, leaving the ethylated body in solution, plus a small percent of tarry matter. The solution

was diluted to 200 c.c. with water, and the tarry matter filtered off through a wet filter.

REDUCTION OF P-NITROPHENETOL TO P-AMINOPHENETOL

This operation consists in replacing the two molecules of oxygen on the nitro-group by two molecules of hydrogen, according to the following equation:-



The first reference to the fact that the reduction of aromatic nitro-compounds to the corresponding amino-derivatives through the agency of tin and hydrochloric acid often leads to the production of by-products containing chlorine, was made by Fittig (Ber. 1875 8:15.)

Those who have used this method of reduction cannot have failed to notice the production of these halogenated by-products. Very few attempts have been made either to identify them or to work out an experimental basis for their formation.

Desiring to avoid the formation of these chlorinated halogens, the authors have substituted iron filings for tin,and dilute acid

for concentrated acid. By this process these halogenated by-products are not formed.

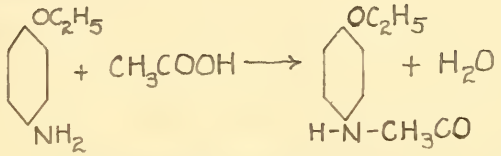
The solutions of p-nitrophenetol were gently warmed on the water bath in 500 c.c. Erlenmeyer flasks, each containing fifteen grams iron filings and 60 c.c. 1:2 hydrochloric acid. When the reaction of the iron and acid began, the solution was colored a purplish-black. The flasks were then removed from the water bath and allowed to stand for twelve hours, at the end of which time reduction was deemed complete. The p-aminophenetol is soluble in dilute acid solution, and was therefore, easily separated from the murky precipitate and residual iron filings by filtering and washing the precipitate several times with boiling water.

Acetphenetidin, when prepared by reducing the p-nitrophenetol with concentrated acid and tin, melts below 100°C, and on investigation, showed that it contained about equal quantities of Acetphenetidin (m.p. 136°C) and chloro-acetphenetidin (m.p. 97°C.) (J.Chem.Soc.107)

Subsequently, it was found that pure Phenacetin was formed by using dilute acid, as carried on by the authors.

ACETYLATION OF P-AMINOPHENETOL TO P-ACETPHENETIDIN

This step is accomplished by replacing one molecule of hydrogen in the amino group by acetyl group CH CO according to the following reaction:-



The acid solutions of p-aminophenetol were heated in erlenmeyer flasks under a reflux condenser, on the water bath, with 60 c.c. of glacial acetic acid for eight hours. At the end of that time the excess of acetic acid was evaporated off, the residue extracted three times with 100 c.c. alcohol by heating on a water bath under a reflux condenser for one-half hour. The contents of the flask were then washed on to a filter paper with hot water. The filtrate contained the Acetphenetidin. The filtrate was diluted with tin times its bulk of water and the excess

alcohol evaporated off on a water bath. The water solution was further concentrated to a small bulk, when light yellow crystals appeared on the surface. The solution was allowed to stand twelve hours; and long, light yellow needles crystallized out. At this stage it was decided to make identification tests for Acetphenetidin to ascertain the nature of the crystals. These tests showed the presence of Acetphenetidin contaminated with sodium acetate.

The next problem was to extract the pure crystals of Acetphenetidin from the sodium acetate. It was decided to extract with glycerol, in which Acetphenetidin is soluble. A small quantity of the contaminated crystals were extracted with glycerol, diluted with hot water and evaporated down on the water bath. The crystals which separated out on cooling, were identified as Acetphenetidin by the following tests. Owing to the lack of time, the authors were compelled to bring their investigation to a close at this juncture.

IDENTIFICATION TESTS FOR ACETPHENETIDIN.

Melting point test :- 133°C.

The true melting point of Acetphenetidin is 135°C.

The crystals were soluble in alcohol, glycerol, very slightly soluble in cold water, and dissolved in hot water in a ratio about 1:50.

A few of the crystals were boiled with concentrated hydrochloric acid, diluted, and to the filtrate was added two to three drops of potassium dichromate solution. A ruby red color was produced. This is a commercial test for pure Acetphenetidin.

After boiling the foregoing filtrate, it was filtered, and a drop of bromine water added. The solution remained clear. This is a follow up test of the potassium dichromate method.

THE MANUFACTURE OF ACETPHENETIDIN FROM PHENOL.

C O N C L U S I O N.

As a result of their investigations, the authors believe that the Manufacture of Acetphenetidin from Phenol by this method is not of commercial importance for the following reasons:-

The small yield of p-nitrophenol from the nitration of Phenol, in comparison with other, more economical methods.

The inability, because of characteristics of the reaction, to obtain products which shall be free from halogenated by-products and residual tarry matter.

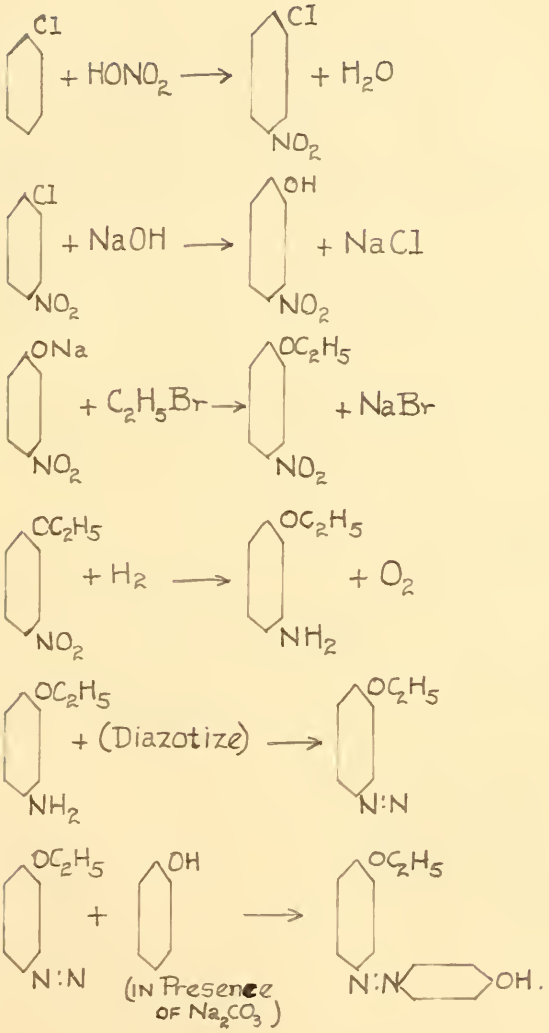
Because more satisfactory methods can be worked out and are now being used, one of which methods the authors would suggest as worthy of further investigation.

Para-nitrophenol is prepared by nitrating chlorbenzol with concentrated nitric acid to

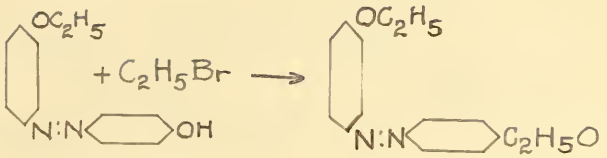
to form mono-nitro chlorbenzol. This body is then heated with caustic soda to form p-nitrophenol. In this way a fairly representative yield of p-nitrophenol is obtained.

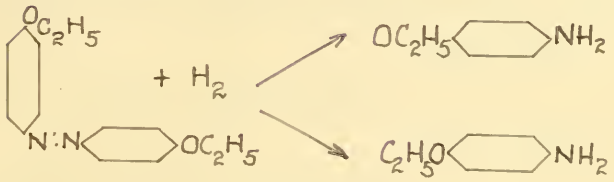
One molecule of p-nitrophenol is made to furnish a large number of molecules of Acetphenetidin by converting the p-nitrophenol to p-phenetidin, diazotizing, and coupling with Phenol in the presence of sodium carbonate. This body is then ethylated, and the product obtained is reduced, whereby two molecules of p-phenetidin are obtained. These, then can be converted to Acetphenetidin by acetylation, or can be made to yield a double quantity of p-phenetidin by repeating the above process of diazotizing and coupling with Phenol. The above process can, of course, be repeated as often as desired. These reactions are as shown by the following equations:-

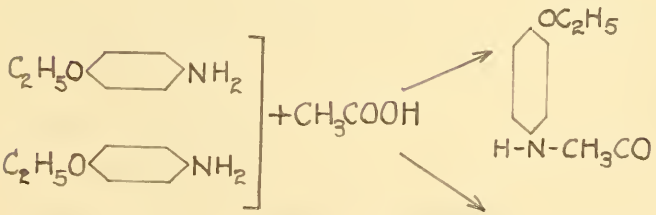
E Q U A T I O N.S


Cl
+ HONO2
Cl
NO2
+ H2O
Cl
NO2
+ NaOH
OH
NO2
+ NaCl
ONa
NO2
+ C2H5Br
OC2H5
NO2
+ NaBr
CC2H5
NO2
+ H2
OC2H5
NH2
+ O2
OC2H5
NH2
+ (Diazotize)
OC2H5
N:N
OC2H5
N:N
+
OH
(IN Presence OF Na2CO3)
OC2H5
N:N
OH.

EQUATIONS.







THIS MOLECULE IS MADE TO YIELD A DOUBLE QUANTITY OF P-PHENETIDIN.

APPENDIX

B I B L I O G R A P H Y.

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L I T E R A T U R E.

The investigation of current literature and texts, by the authors, revealed no treatise on the details of Manufacture of Acetphenetidin, giving only the general, well-known reaction and equations.

A systematic investigation was made of the following literature:-

Journal of the Society of Chemical Industry. (Abstracts, Transactions and Proceedings.)

Journal of the American Chemical Society.

Chemical Abstracts.

Journal für praktische Chemie.

Pharmaceutical Journals.

Pharmazeutische Zeitung.

Berichte der Deutschen Pharmazeutischen Gesellschaft.

Berichte der Deutschen Chemischen Gesellschaft.